



General

Guideline Title

Chemotherapy (i.e., gemcitabine, docetaxel plus gemcitabine, doxorubicin, or trabectedin) for inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma.

Bibliographic Source(s)

Gupta A, Yao X, Verma S, Mackay H, Hopkins L, Sarcoma Disease Site Group (DSG), Gynecology Cancer DSG. Chemotherapy (i.e., gemcitabine, docetaxel plus gemcitabine, doxorubicin, or trabectedin) for inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma. Toronto (ON): Cancer Care Ontario (CCO); 2012 Jul 18. 41 p. (Evidence-based series; no. 11-11). [37 references]

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

Recommendations

Major Recommendations

Recommendations and Key Evidence

In the absence of randomized controlled trials (RCTs) comparing chemotherapy with no treatment controls for inoperable, recurrent, or metastatic leiomyosarcoma (LMS) of the uterus, the Sarcoma Disease Site Group (DSG) and Gynecologic Cancer DSG offer the following recommendations:

- Doxorubicin alone or gemcitabine alone or gemcitabine plus docetaxel may be treatment options as first and/or second line therapy for women with inoperable, locally advanced, recurrent, or metastatic uterine LMS, based on current available evidence from the medical literature (four single-arm phase II studies, one arm of an RCT, and one abstract).
 - Hematological toxicity is common and should be monitored, and granulocyte growth factor (G-CSF) should be considered when gemcitabine plus docetaxel is used.
 - Other toxicities, such as neurotoxicity, pulmonary or cardiovascular toxicity, should be monitored.
- No recommendation is made for or against using trabectedin in the targeted patients.

- Patients should be encouraged to participate in clinical trials testing novel or targeted approaches in this disease.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma (LMS)

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Internal Medicine

Obstetrics and Gynecology

Oncology

Radiation Oncology

Surgery

Intended Users

Pharmacists

Physicians

Guideline Objective(s)

To evaluate the appropriateness of chemotherapy (i.e., gemcitabine, docetaxel plus gemcitabine, doxorubicin, or trabectedin) for inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma (LMS)

Target Population

Women with inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma (LMS)

Interventions and Practices Considered

1. Doxorubicin alone
2. Gemcitabine alone
3. Gemcitabine plus docetaxel
4. Consideration of granulocyte growth factor (G-CSF)

5. Monitoring for hematological toxicity, neurotoxicity, pulmonary or cardiovascular toxicity

Note: Trabectedin was considered but not recommended.

Major Outcomes Considered

- Overall and progression-free survival time
- Tumour response rate (the sum of the complete response and partial response rate)
- Stable disease rate
- Progressive disease rate
- Toxicity

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Strategy

In 2004, Program in Evidence-based Care (PEBC) and the Gynecologic Cancer Disease Site Group (DSG) developed a guideline on systemic therapy for advanced, recurrent, or metastatic uterine sarcoma by searching the literature from 1980 to June 2004. This 2004 systematic review was used as the basis for this new updated review. Because the 2005 guideline included studies pertaining to all types of uterine sarcoma, only those that met the study selection criteria of this new guideline were eligible for inclusion in this review.

To update the 2004 systematic review, a literature search was performed using MEDLINE and EMBASE through the Ovid search engine from January 1, 2004, to June 17, 2011 to find eligible full texts. The search strategies are reported in Appendices 2 and 3 of the original guideline document. The following resources were checked for existing systematic reviews and practice guidelines, based on a systematic review: the Cochrane Library (to Issue 6, 2011), National Guideline Clearinghouse, National Health and Medical Research Council (Australia), New Zealand Guidelines Group, American Society of Clinical Oncology, National Comprehensive Cancer Network, National Institute for Health and Clinical Excellence, Scottish Intercollegiate guidelines Network, Society of Obstetricians and Gynaecologists of Canada, and Gynecologic Oncology Group (to June 16, 2011); and the Standards and Guidelines Evidence Inventory of Cancer Guidelines, which included over 1100 English-language cancer control guidelines and standards released from 2003 through June 2010 when it was checked on June 2, 2011.

The American Society of Clinical Oncology (ASCO) Annual Meeting Abstracts from 2005 to 2011 and Connective Tissue Oncology Society (CTOS) Annual Meeting Abstracts from 2005 to 2010 were checked for eligible abstracts.

Study Selection Criteria

Inclusion Criteria

Articles or abstracts were eligible for inclusion in this systematic review if they met all of the following criteria:

1. Full text reports were published from January 1, 2004, to June 17, 2011 or abstracts were published from January 1, 2005, to July 7, 2011.
2. Full text reports were systematic reviews, clinical practice guidelines based on a systematic review, randomized controlled trials (RCTs), or prospective studies; or published abstracts that were RCTs that investigated the effect of either gemcitabine, doxorubicin, or trabectedin alone, or in a combination of gemcitabine plus docetaxel.
3. Full text reports or abstracts reported at least one of the following clinical outcomes: tumour response rate, overall survival (OS), toxicity,

progression-free survival (PFS), or quality of life (QOL) in women with inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma (LMS).

4. Studies reported at least one relevant outcome on 20 or more target patients.

Exclusion Criteria

Articles or abstracts were excluded if they met any of the following criteria:

1. Full text reports or abstracts were published in a language other than English.
2. They were non-systematic reviews, animal studies, letters, editorials, or commentaries.
3. Studies enrolled uterine LMS patients and other types of sarcoma patients but did not report any relevant outcome separately for uterine LMS patients.

Number of Source Documents

Five full texts and 1 abstract were included in the systematic review.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Synthesizing the Evidence

If possible, a meta-analysis of each clinical outcome would be considered and conducted. Any data for which denominators were less than 30 should be considered carefully because they usually have an extremely large 95% confidence interval (CI) and are unlikely to be statistically significant.

STATA 11.0 would be the statistical software for statistical calculation purposes and for producing figures. A two-sided significance level of $\alpha = 0.05$ was assumed.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Methods

The Evidence-based Series (EBS) guidelines developed by the Program in Evidence-based Care (PEBC) use the methods of the Practice Guidelines Development Cycle. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by the Working Group, which included three Disease Site Group (DSG) members and one methodologist from the

PEBC (see Appendix 1 in the original guideline document). All data were audited by a second, independent auditor. The available medical literature evidence forms the basis of the recommendations developed by the Sarcoma DSG and the Gynecology Cancer DSG, which are published in Section 1 in the original guideline document.

Development and Internal Review

This EBS was developed by the Sarcoma and Gynecology DSGs of the Cancer Care Ontario (CCO) PEBC. The series is a convenient and up-to-date source of the best available evidence on chemotherapy (i.e., gemcitabine, docetaxel plus gemcitabine, doxorubicin, or trabectedin) for inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma, developed through a review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Report Approval Panel

Prior to the submission of this Evidence-Based Series (EBS) draft report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel (RAP), which consists of three members, including two oncologists, with expertise in clinical and methodology issues, and a methodologist.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two pronged and includes a targeted peer review intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Guideline Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the guideline authors circulated Sections 1 and 2 to external review participants for review and feedback.

Methods

Targeted Peer Review

During the guideline development process, 10 targeted peer reviewers from North America considered to be clinical and/or methodological experts on the topic were identified by the guideline authors. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on March 23, 2012. Follow-up reminders were sent at two weeks and at four weeks. All the targeted peer reviewers were required to complete the conflict of interest form.

Professional Consultation

65 potential participants were identified by the guideline authors. Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on March 23, 2012. Two follow-up reminders were sent on April 9 and April 23, 2012.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Sarcoma Disease Site Group (DSG), the Gynecology Cancer DSG, and the Working Group.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by randomized and non-randomized trials.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of chemotherapy (i.e., gemcitabine, docetaxel plus gemcitabine, doxorubicin, or trabectedin) for inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma (LMS)

Potential Harms

Adverse effects of chemotherapy include leucopenia, thrombocytopenia, neurotoxicity, cardiovascular toxicity, and pulmonary toxicity. See the table on page 2 of the original guideline document for information on toxicities of specific drug regimens.

Qualifying Statements

Qualifying Statements

- The following chemotherapy agent doses were suggested from the included studies:
 - Doxorubicin: 60-80 mg/m² intravenously (IV) every 3 weeks
 - Gemcitabine: 1000 mg/m² IV on days 1, 8, and 15 every 4 weeks
 - Gemcitabine plus docetaxel: gemcitabine 900 mg/m² IV on days 1 and 8, followed by docetaxel 100 mg/m² IV on day 8 every 3 weeks.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario (CCO) makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Gupta A, Yao X, Verma S, Mackay H, Hopkins L, Sarcoma Disease Site Group (DSG), Gynecology Cancer DSG. Chemotherapy (i.e., gemcitabine, docetaxel plus gemcitabine, doxorubicin, or trabectedin) for inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma. Toronto (ON): Cancer Care Ontario (CCO); 2012 Jul 18. 41 p. (Evidence-based series; no. 11-11). [37 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Jul 18

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Guideline Committee

Sarcoma Disease Site Group and Gynecology Cancer Disease Site Group

Composition of Group That Authored the Guideline

Working Group Members: Dr. Abha Gupta, Medical Oncologist, Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, Ontario; Dr. Shailendra Verma, Medical Oncologist, Department of Medical Oncology, The Ottawa Hospital Regional Cancer Centre, Ottawa, Ontario; Dr. Helen Mackay, Medical Oncologist, Department of Medical Oncology, UHN Princess Margaret Hospital, Toronto, Ontario; Dr. Laura Hopkins, Gynecological Oncologist, Department of Obstetrics and Gynecology, The Ottawa Hospital, Ottawa, Ontario; Ms. Xiaomei Yao, Research Coordinator, Program in Evidence-based Care, Cancer Care Ontario, Hamilton, Ontario

Sarcoma DSG Members: Dr. Jordi Cisa, Surgical Oncologist, Department of Orthopaedic Surgery, Laurentian Hospital, Sudbury, Ontario; Dr. Thomas Corbett, Assistant Clinical Professor, Division of Radiation Oncology, Department of Oncology, McMaster University, Hamilton, Ontario; Dr. Gina Di Primio, Radiologist, Department of Radiology, The Ottawa Hospital Regional Cancer Centre, Ottawa, Ontario; Dr. Jay Engel, Surgical Oncologist, Department of Surgical Oncology, Cancer Centre of Southeastern Ontario, Kingston, Ontario; Dr. Michelle Ghert, Surgical Oncologist, Department of Orthopaedic Surgery, Juravinski Cancer Centre, Hamilton, Ontario; Dr. Rita Kandel, Pathologist, Department of Pathology & Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario; Carol Swallow, Surgical Oncologist, Department of Surgical Oncology, Princess Margaret Hospital, Toronto, Ontario; Dr. Joel Werier, Surgical Oncologist, Department of Orthopaedic Surgery, The Ottawa Hospital Regional Cancer Centre, Ottawa, Ontario; Dr. Jawaid Younus, Medical Oncologist, London Regional Cancer Care Program, London Health Sciences Centre, London, Ontario

Gynecology Cancer DSG Members: Dr. Allan Covens, Head of Gynaecologic Oncology, Department of Obstetrics and Gynaecology, Sunnybrook Health Sciences Centre, Toronto, Ontario; Dr. Anthony Fyles, Professor, Department of Obstetrics and Gynecology, University of Toronto, Toronto, Ontario; Dr. Barry Rosen, Gynecologic oncologist, Department of Gynecology-Oncology, Princess Margaret Hospital, Toronto, Ontario; Dr. Elit Laurie, Gynecologic Oncologist, Juravinski Cancer Centre, Hamilton Health Sciences, Hamilton, Ontario; Dr. Julie Ann Francis, Gynaecological Oncologists, Department of Obstetrics and Gynecology, Queen's University, Kingston, Ontario; Dr. Hirte Hal, Associate Professor, Department of Oncology - Division of Medical Oncology, McMaster University, Hamilton, Ontario; Dr. Jason Dodge, Assistant Professor, Division of Gynecologic Oncology, Department of Obstetrics and Gynaecology, University of Toronto; Dr. Liz Strevel, Medical Oncologist, Department of Medical Oncology, Mississauga, Ontario; Dr. Michael Fung Kee Fung, Professor, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology and Department of Surgery, University of Ottawa, Ottawa, Ontario; Dr. Michel Prefontaine, Gynecologic Oncologist, London Health Sciences Centre, London, Ontario; Dr. Tien Le, Gynecological Oncologist, Head of Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Ottawa/Ottawa Regional Cancer Centre, Ottawa Ontario

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest (COI) Policy, the guideline authors, the Sarcoma and Gynecologic Cancer Disease Site Group (DSG) members, and the internal and targeted external reviewers were asked to disclose potential conflicts of interest.

The five guideline authors declared they had no conflicts.

One Sarcoma DSG member, CS, declared conflicts and reported receiving \$10,000 or less as honoraria for speaking at annual meetings and \$10,000 for mutational analysis for gastrointestinal stromal tumour from Novartis Oncology; other Sarcoma DSG members had no conflicts of interest. The Gynecologic Cancer DSG members declared they had no conflicts of interest.

The PEBC Assistant Director (HM) and two Research Coordinators (EK and CA) declared that they had no conflicts of interest.

The three RAP members (WE, SH, and MB) declared that they had no conflicts of interest.

For the three targeted external reviewers, none of them had COI.

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy.

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#) .

Availability of Companion Documents

The following are available:

- Chemotherapy (i.e., gemcitabine, docetaxel plus gemcitabine, doxorubicin, or trabectedin) for inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2012 Jul 18. 8 p. Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#) .
- Program in Evidence-based Care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Available in PDF from the [Cancer Care Ontario Web site](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on April 10, 2014. This summary was updated by ECRI Institute on July 18, 2014 following the U.S. Food and Drug Administration advisory on Docetaxel.

Copyright Statement

This NGC summary is based on the original guideline, which is subject to the guideline developer's copyright restrictions. Please refer to the [Copyright and Disclaimer Statements](#) posted at the Program in Evidence-based Care section of the Cancer Care Ontario Web site.

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouse^{â„¢} (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at <http://www.guideline.gov/about/inclusion-criteria.aspx>.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.